A Simple Ansatz to Describe Thermodynamic Quantities of Peptides and Proteins at Low Temperatures

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ABSTRACT

We describe a simple ansatz to approximate the low temperature behavior of proteins and peptides by a mean-field-like model which is analytically solvable. For a small peptide some thermodynamic quantities are calculated and compared with numerical results of an all-atoms simulation. Our approach can be used to determine the weights for a multicanonical simulation of the molecule under consideration.

Key words: Mean-field-like model for proteins, Multicanonical weights.

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Prediction of the three-dimensional structure of peptides and proteins solely from their amino-acid sequence remains one of the longstanding unsolved problems in bioscience. It is widely accepted that the three-dimensional shape at temperature T corresponds to the global minimum in *free* energy of the molecule. Therefore, given a sufficiently accurate description of the intramolecular forces, it should be in principle possible to predict such conformations through a numerical simulation. However, the complex form of the interactions containing both repulsive and attractive terms leads to a very rough energy landscape with a huge number of local minima separated by high energy barriers. These barriers slow down the ergodic exploration of conformation space at low temperatures. In the canonical ensemble at temperature T, the probability to cross an energy barrier of height ΔE is proportional to $e^{-\Delta E/k_BT}$. Hence, at low temperatures, canonical molecular dynamics and Monte Carlo, using local updates, will get trapped in one of these local minima. Within limited simulation time, only small parts of phase space are sampled and physical quantities cannot be calculated accurately.

However, with the development of the multicanonical approach [1], simulated tempering [2] and other *generalized-ensemble* techniques, an efficient sampling of low energy configurations and an accurate calculation of thermodynamic quantities at low temperatures became feasible, at least for small peptides. The first application of one such technique to the protein folding problem can be found in Ref. [3]. Later applications include the study of the coil-globular transitions of a model protein [4] and the helix-coil transitions of homo-oligomers of nonpolar amino acids [5]. A numerical comparison of several generalized-ensemble algorithms can be found in Ref. [6]. Nevertheless, calculation of thermodynamic quantities by numerical simulations remains a time consuming process. The evaluation of energies which is necessary for each Monte Carlo or molecular dynamics step is itself CPU time intensive. Hence, it is desirable to find an approximate description of the thermodynamic properties of complicated molecules like peptides by using a much simpler effective model. The form of the effective model should retain the essential physical characteristics of the original system (number and nature of the degrees of freedom) and its parameters be adjusted to best reproduce the thermodynamic properties of the original, especially at low temperature. The results from generalized ensemble

simulations now allow the development and testing of such an approach.

Fixing bond lengths and bond angles (which within our range of temperatures can be considered as rigid), peptides and proteins can be described by a set of torsion angles. This is the motivation behind our choice to describe our effective model by n_F independent angles θ_i , i = 1, ..., n, where $\theta_i \in [-\pi, \pi[$. We assume that the potential energy of our system can be approximated by

$$E \approx \sum_{i}^{n_F} V(\theta) , \qquad (1)$$

where the "mean" potential $V(\theta)$ is the same for each angle. The most general form for the periodic potential V is

$$V(\theta) = \sum_{k=0}^{\infty} a_k \cos k\theta + b_k \sin k\theta \tag{2}$$

Without loss of generality, we can impose that the global minimum of V occurs, for instance, at $\theta = 0$. Then the low-temperature behavior will be determined by the harmonic approximation

$$V_{harmonic}(\theta) = c_0 + c_1(1 - \cos \theta) . \tag{3}$$

To maintain the simplicity of our effective model, we truncate the expansion in Eq. (2) to

$$V(\theta) = c_0 + c_1(1 - \cos \theta) + c_2(1 - \cos \theta)^2$$
(4)

with anharmonic term c_2 . The 3 parameters c_0, c_1 , and c_2 will be fitted to best match features of the original model. It is obvious that

$$c_0 = \frac{E_{GS}}{n_F} \tag{5}$$

where E_{GS} is the ground state energy of our molecule.

The partition function of our effective model is simply

$$Z = z^{n_F}$$
 with $z = \int_{-\pi}^{+\pi} d\theta e^{-\beta V(\theta)}$ (6)

Using the definition of the modified Bessel function $I_n(y) = \frac{1}{\pi} \int_0^{\pi} dx \cos nx \ e^{y \cos x}$, and the identity $e^{y \cos x} = I_0(y) + 2 \sum_{k=1}^{\infty} I_k(y) \cos kx$, the partition function per angle z can be expressed as

$$z = 2\pi e^{-\beta(c_0 + c_1 + \frac{3}{2}c_2)} \left(I_0(-\beta c_2/2)I_0\left(\beta(c_1 + 2c_2)\right) + 2\sum_{k=1}^{\infty} I_k(-\beta c_2/2)I_{2k}\left(\beta(c_1 + 2c_2)\right) \right)$$
(7)

The average energy < E > can be obtained through $< E > = -d(\log Z)/d\beta$, or directly as

$$\langle E \rangle = \left[(c_0 + c_1 + \frac{3}{2}c_2) - (c_1 + 2c_2) \langle \cos x \rangle + \frac{c_2}{2} \langle \cos 2x \rangle \right] n$$
 (8)

with

$$\langle \cos mx \rangle = f(m)/f(0) \tag{9}$$

$$f(m) \equiv I_0(-\beta c_2/2)I_m (\beta(c_1 + 2c_2))$$
(10)

+
$$\sum_{k=1}^{\infty} I_k(-\beta c_2/2) \left[I_{2k+m} \left(\beta(c_1 + 2c_2) \right) + I_{2k-m} \left(\beta(c_1 + 2c_2) \right) \right]$$
 (11)

and similarly for the specific heat which we define as

$$C(T) = \frac{1}{k_B n_A} \frac{\mathrm{d}}{\mathrm{d}T} < E > \tag{12}$$

with Boltzmann constant k_B and n_A the number of residues.

We expect Eq. 1, with the mean potential given by Eq. 4, to be a good approximation of our system for low temperatures. In principle the approximation can be systematically improved for higher temperatures by increasing the number of terms in the expansion of Eq. 2. However, this will lead to more complicated equations than for instance Eqs. 7 and 8. While periodicity of the variables θ is not required for a low-temperature approximation, this similarity with the original system improves the quality of the approximation at higher temperatures (e.g. the specific heat remains bounded).

Our benchmark is one of the simplest peptides, Met-enkephalin, which has become an often used model to examine new algorithms in the protein folding problem. Met-enkephalin has the amino acid sequence Tyr-Gly-Gly-Phe-Met. For comparison and to fit the free parameters of our ansatz we use the results published in Ref. [7]. They were derived from a multicanonical simulation of 200,000 sweeps using a potential energy function E_{tot} given by the sum of electrostatic term E_C , Lennard-Jones term E_{LJ} , and hydrogen-bond term E_{hb} for all pairs of atoms in the peptide together with the torsion term E_{tors} for all torsion angles. The parameters for the energy function were adopted from ECEPP/2 [8]. By fixing the peptide bond angles ω to 180°, 19 torsion angles were left as degrees of freedom (i.e. $n_F = 19$).

In our ansatz using Eq. 7 to approximate our molecule we have three free parameters which have to be fitted against numerical results. Since our approximation is only valid for low temperatures, we should perform the fit against results at the lowest reliable temperatures available. We expect canonical simulations of peptides and proteins to be computationally feasible down to the folding temperature T_F . A fit of our free parameters should therefore be done against thermodynamic quantities measured in the vicinity of this temperature. By using results from simulated annealing runs it may be possible to include results of even lower temperatures. In our case, however, we restricted ourselves to the temperature range 200 K to 240 K, since the folding temperature was found to be $T_F \approx 220~K$ for Met-enkephalin [9]. For our fit in this temperature range we use results for the average energy $\langle E \rangle$ and specific heat C(T) as obtained from a multicanonical simulation and published in Ref. [7]. We find $c_0 = -0.55$ kcal/mol, $c_1 = 4.77$ kcal/mol and $c_2 = -2.05$ kcal/mol. These parameters were obtained in the following way. Since one shortcoming of our ansatz is to underestimate the peak in the specific heat, we first fixed the ratio c_2/c_1 to the value -0.43 which gives the highest specific heat peak. Then we adjusted c_1 to reproduce the specific heat in the chosen temperature range 200 K to 240 K. Finally the remaining parameter c_0 was fixed by requiring that our fit reproduce the values for the average energy $\langle E \rangle$ in the chosen temperature range. For the case of a pure harmonic approximation, i.e. fixing $c_2 = 0$, we were not able to obtain a fit which would reproduce $\langle E \rangle$ and C(T) in the temperature range 200 K to 240 K. The closest low-temperature match was obtained for a choice of parameters $c_0 = -0.55$ kcal/mol and $c_1 = 1.19 \text{ kcal/mol}$. We remark that $n_F c_0$ is an estimate for the ground state energy. Hence, the value of $n_F c_0 \approx -10.5$ kcal/mol should be compared with the known true value of $E_{GS} = -10.72 \text{ kcal/mol.}$

Using the above values for c_i we were now able to calculate estimates for the average energy $\langle E \rangle$ and specific heat C(T) by our ansatz and compare the obtained results with those of a multicanonical simulation. In Fig. 1 we display $\langle E \rangle$ and in Fig. 2 the specific heat C(T) as obtained by our ansatz (with and without anharmonicity constant c_2) and by a multicanonical simulation. As one can clearly see from our data, it is necessary to include anharmonic terms in our ansatz. A pure harmonic approximation

produces reasonable values for the average energy $\langle E \rangle$ only for temperatures below 150 K and for the specific heat below $T \sim 90$ K. Including an anharmonicity constant c_2 dramatically improves the ability of our ansatz to predict average energies. Values for this quantity can now be reproduced up to temperatures ≈ 300 K, i.e. to temperatures where usual canonical Monte Carlo simulations are feasible. However, our approach is less successful for the specific heat, where the data from the multicanonical simulation can only be reproduced up to temperatures ≈ 220 K, the folding temperature T_F . Better agreement could be obtained with the addition of further anharmonic terms.

We have demonstrated that for small peptides the low temperature behavior of energy and related quantities can be described by our simple ansatz. In addition, our ansatz can also be used to obtain estimators for the weights in generalized-ensemble simulations. Unlike for the canonical ensemble these weights are not a priori known, and a great fraction of the computing effort (about 1/2) goes into their determination prior to the simulation itself. As an example take the multicanonical algorithm. Here, the weights are defined by

$$w_{mu}(E) \propto n^{-1}(E) = e^{-S(E)} ,$$
 (13)

where n(E) is the spectral density and S(E) the microcanonical entropy. Obviously, knowledge of the weights in this ensemble is equivalent to that of the spectral density, i.e. to solving the system. Hence, the need for estimators. Usually these estimators are calculated by an iterative procedure, first described in Ref. [1]. However, convergence of this method depends strongly on the model under consideration, and determining the weights can be a time consuming and difficult process. Several attempts have been made to speed up their calculation, see for instance Refs. [10, 11, 12], but there is still need for further improvement. Here, we propose to take as estimators for the multicanonical weights

$$w_{mu}(E) \propto \tilde{n}^{-1}(E) = e^{-\tilde{S}(E)} ,$$
 (14)

where $\tilde{n}(E)$ ($\tilde{S}(E)$) is the spectral density (microcanonical entropy) of our effective model. Note that once multicanonical weights are known, it is easy to calculate the weights for other generalized ensemble techniques as was shown in Ref. [13]. In principle, $\tilde{n}(E)$ can be calculated directly from the partition function Eq. 6. However, in practice it is easier to calculate the canonical entropy

$$\tilde{S}(T) = \frac{\langle E \rangle (t)}{k_B T} + \log Z(T) , \qquad (15)$$

and approximate $\tilde{S}(E) \approx \tilde{S}(T[\langle E \rangle])$. The function $\langle E \rangle (T)$ can be calculated by our ansatz, which allows us in turn to obtain $T(\langle E \rangle)$. This approximation of the microcanonical entropy by the canonical one becomes exact for $n_F \longrightarrow \infty$.

With the above ansatz we were able to calculate new multicanonical weights for Metenkephalin, for energies between -10.7 and 0 kcal/mol. The upper limit comes from the fact that our approach gives a good approximation of the average energy only for $T \leq 300~K$, where $< E > (T = 300~K) \approx 0$. For higher energies we set $w(E) = c \cdot e^{-E/(300 \cdot k_B)}$ where the constant c is chosen such that the weights are a continuous function of the energy at E = 0. In this way we also allow sampling of high energy states. However, it is clear that with so defined weights use of the re-weighting techniques is essentially restricted to temperatures $T \leq 300~K$. Re-weighting to higher temperatures would lead to expectation values hampered by increasing errorbars since the sampling of configuration becomes poorer and poorer with increasing energies for E > 0.

We used for the calculation of multicanonical weights our full 3-parameter ansatz. since the harmonic approximation fails already at much lower temperatures (and hence energies). In Fig. 3 we show the distribution in energy obtained from a simulation with 1,000,000 sweeps using these weights. The distribution covers the chosen energy range and is essentially flat in this range. The histogram entries for the energies differ by no more than a factor 2. This near-constancy demonstrates that the entropy Eq. 15 of our ansatz is a very good approximation of the exact microcanonical entropy, yielding good estimators for the multicanonical weights. The quality of these estimators and the range of energies could easily be enhanced by further iterations with the method described first in Ref. [1]. However, since our simulation covers a broad range of energies, we can use standard reweighting techniques [14] and obtain already with the given weights accurate thermodynamic quantities over a range of temperatures not accessible by canonical simulations. As an example we show in Fig. 4 the average end-to-end distance < D > (T) (measured from N of Tyr 1 to O of Met 5) as a function of temperature as obtained from

the above multicanonical simulation with the new weights. This quantity is a simple measure for the compactness of configurations. For comparison we also show the results from a multicanonical simulation with the same number of sweeps but with the more constant weights used in Ref. [7]. As one can clearly see the two sets of weights lead to values of the end-to-end distance compatible with each other. Note that in the case of the new weights the errorbars increase rapidly with temperature for T > 300 K, reflecting the fact that for $E \ge 0$ configurations are no longer sampled according to a uniform distribution but to a Boltzmann distribution at T = 300 K. On the other hand, the old set of weights yields a flat distribution for energies up to ≈ 20 kcal/mol (which corresponds to T = 1000K) and therefore the size of errorbars does not increase with temperature in the shown range of temperatures.

For a study of the protein folding problem one would prefer proteins which are at least an order of magnitude larger than Met-enkephalin, the peptide we used in this work. It is difficult to predict how useful our ansatz is going to be in this case. On the one hand one expects a statistical, mean-field description to be even more accurate on a larger system. On the other hand, a larger protein will have a more pronounced folding transition, becoming first-order-like (for a discussion on the nature of the folding transition see, for instance, Ref. [15]), and this collective phenomenon will be impossible to capture with our mean-field approach. Therefore we would expect our ansatz to work better below the folding temperature T_F , more poorly at or above it. Its efficiency for the determination of multicanonical weights remains to be determined.

To summarize our results, we have introduced a simple mean-field-like model to describe the low temperature behavior of peptides and proteins, which can be systematically improved by including higher Fourier components in the mean-field potential. For a small peptide we calculated some thermodynamic quantities and compared the results with the ones from an all-atoms simulation. In addition, our ansatz allows for peptides a simple and efficient calculation of multicanonical weights alleviating in this way the main drawback of these techniques.

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Figures:

- 1. Average energy $\langle E \rangle$ as a function of temperature. Shown are the results obtained from our ansatz, for both $c_2 = 0$ (dot dashed line) and $c_2 \neq 0$ (unbroken line). For comparison we also show the results obtained from a multicanonical run of 200,000 sweeps (marked by +).
- 2. Specific heat C(T) as a function of temperature. Shown are the results obtained from our ansatz, for both $c_2 = 0$ (dot dashed line) and $c_2 \neq 0$ (unbroken line). For comparison we also show the results obtained from a multicanonical run of 200,000 sweeps (marked by +).
- 3. Multicanonical distribution of energy, $P(E) \propto e^{-S(E)+\tilde{S}(E)}$, obtained from a multicanonical simulation of 1,000,000 sweeps with weights calculated from our ansatz.
- 4. Average end-to-end-distance $\langle D \rangle_T$ as a function of temperature. The data marked by \diamond are from a multicanonical simulations of 1,000,000 sweeps with weights obtained by our new ansatz. For comparison we also show the results (marked by +) from a multicanonical simulation with same number of MC sweeps and the weights of Ref. [7] which were obtained by the older iterative procedure.







